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BDNF val66met polymorphism is associated with modified experience-dependent plasticity in human motor cortex

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Motor training can induce profound physiological plasticity within primary motor cortex, including changes in corticospinal output and motor map topography. Using transcranial magnetic stimulation, we show that training-dependent increases in the amplitude of motor-evoked potentials and motor map reorganization are reduced in healthy subjects with a val66met polymorphism in the brain-derived neurotrophic factor gene (*BDNF*), as compared to subjects without the polymorphism. The results suggest that *BDNF* is involved in mediating experience-dependent plasticity of human motor cortex.

Motor cortex physiology is highly sensitive to motor experience. Transcranial magnetic stimulation (TMS) experiments in human subjects demonstrate that motor training can induce reorganization of movement representations¹ and enhance corticospinal output². Parallel animal studies show similar changes in cortical function that are mediated by synaptic plasticity within cortical circuitry in response to various neural signals³. *BDNF* has been identified as one of the key neural signals orchestrating synaptic plasticity⁴ and is elevated within motor cortex in response to motor training⁵. A single nucleotide polymorphism producing a valine-to-methionine substitution at codon 66 (val66met) in the human *BDNF* gene is associated with abnormal cortical morphology⁶, memory impairments⁷ and reduced medial temporal lobe activity⁸. We hypothesized that the presence of the val66met polymorphism would be associated with abnormal training-induced motor cortex plasticity.

We recruited 78 healthy, right-handed subjects between the ages of 18 and 29 (mean age 22.7 ± 1.4 years; all subjects provided informed written consent and all procedures were approved by the University of California Irvine Institutional Review Board). We obtained blood samples, and the subjects were genotyped for the *BDNF* val66met polymorphism. We carried out polymerase chain reaction (PCR) amplification of a 274-bp fragment as described previously⁹. We performed mutation screening with denaturing high-performance

liquid chromatography (DHPLC) analysis on Transgenomics WAVE system (Transgenomics)¹⁰. All homozygote mutant DNA samples detected by DHPLC were confirmed by sequencing. From this pool, 11 Val/Met and 6 Met/Met subjects were identified; all agreed to participate in the study. The first 9 Val/Val subjects that agreed to participate were also recruited (Table 1).

Subjects were tested on three fine-motor tasks: maximum finger tapping rate, nine-hole pegboard and pinch-grip strength. On a separate day, we used single-pulse TMS to generate measures of corticospinal output to the first dorsal interosseous (FDI) muscle of the right hand. A T1-weighted volumetric anatomical magnetic resonance image (MRI) scan was sighted to each subject's head using stereotactic software (BrainSight). Surface electromyograms (EMG) were recorded from the right FDI using cup electrodes in a belly-tendon montage with gain = 10,000 and bandpass filters = 30 Hz and 1,000 Hz. A Magstim 200² magnetic stimulator (Magstim) and a figure-of-eight 70-mm stimulation coil were used to apply TMS to the left precentral gyrus. Each stimulation site was guided by a 1-cm² grid superimposed onto a digital image of the cortical surface. The cortical point with the lowest motor threshold (LMT) for FDI was first identified. LMT was determined to the nearest 1% of stimulator output and defined as the point with the lowest intensity required to produce a motor-evoked potential (MEP) ≥ 50 μ V in at least six of ten pulses. At each LMT site, a recruitment curve was generated by delivering ten stimuli at each of four intensity levels (90%, 130%, 110% and 150% of

Table 1 Subject pool characteristics as a function of genotype

	Val/Val	Val/Met	Met/Met
Age in years	23.2 (1.2)	22.4 (0.9)	20.8 (0.8)
Male	4	6	4
Female	5	5	2
Asian	2	5	3
Caucasian	7	5	1
Hispanic	0	1	2
Handedness score	1.9 (0.1)	1.8 (0.1)	1.9 (0.1)
Peg board in s	18.9 (1.0)	19.4 (1.0)	20.9 (0.9)
Finger tapping in taps per 10 s	60.0 (4.6)	57.7 (2.6)	64.6 (1.1)
Pinch grip in kg	21.0 (2.4)	22.8 (1.2)	24.8 (1.6)
LMT as % device output	41.9 (2.2)	42.1 (2.0)	41.8 (2.7)

Genotype frequencies observed in our cohort (Val/Val 0.63, Val/Met 0.29, Met/Met 0.08) were in Hardy-Weinberg equilibrium, given the mixed population from which they were sampled. Mean (\pm s.e.m.) time to complete the nine-hole peg board task, number of finger taps in 10 s and maximum pinch-grip strength. Mean score on Edinburgh scale reflects handedness: -2 = left-handed, 0 = ambidextrous and +2 = right-handed. Mean (\pm s.e.m.) lowest motor threshold (LMT).

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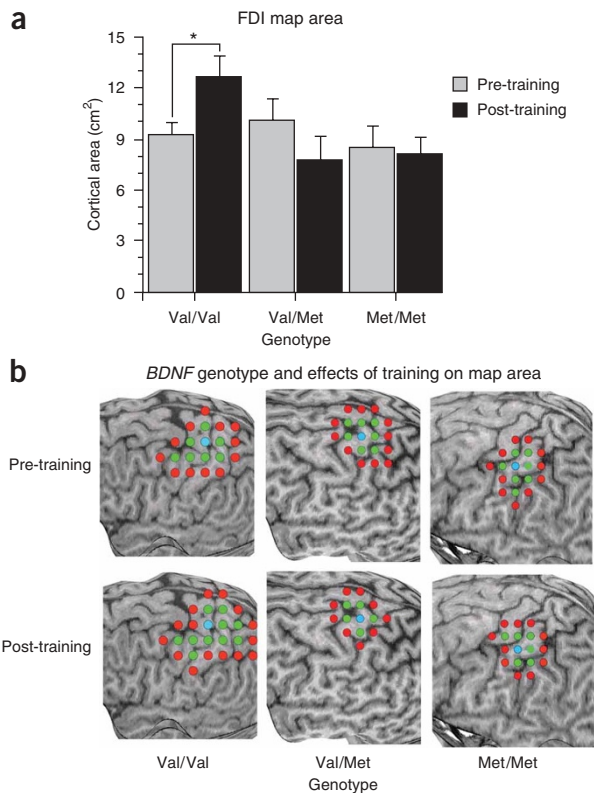


Figure 1 Changes in motor map area with training. **(a)** Mean (\pm s.e.m.) FDI representation area ($*P < 0.05$, Fisher's protected test). **(b)** Representative motor maps of FDI muscle representations from Val/Val, Val/Met and Met/Met subjects superimposed onto a composite MRI image of the cortex. Blue dot, location of the LMT site. Green, positive sites. Red, negative sites.

LMT) in pseudorandomized order. At each intensity, MEP amplitudes were measured and averaged across the ten pulses. After generating this recruitment curve, we systematically applied stimulation (110% LMT) in 1-cm increments across the cortical grid and noted the number of positive responses (3 of 5 MEPs were ≥ 50 μ V). This procedure was continued until each positive site was surrounded by negative sites. The number of positive sites was then used to determine the FDI representation area. We also calculated the center of gravity (COG) and the normalized map volume of the FDI representation¹¹.

Immediately after baseline TMS measures, subjects performed 30 min of FDI exercise: each subject was asked to press the 1 and 3 keys on a keyboard with the right index finger as fast as possible for 15 s, followed by a 15 s break; this was repeated ten times, followed by a 3 min break. Next, subjects adducted the right index finger to press the pad of a pinch-grip gauge (Jamar) every 5 s, reaching at least 5 kg of force, for 5 min; this was followed by a 2 min break. Subjects then performed a second round of each task. We again used TMS to derive a second MEP amplitude recruitment curve, cortical representational area, normalized map volume and center of gravity, using the same LMT value and site as in

the mapping before the FDI exercise. The percentage change in MEP amplitude after training was calculated at 110%, 130% and 150% LMT.

One-way analysis of variance showed no significant effect of genotype on peg-board time ($F_{2,23} = 0.29$; $P = 0.750$), tapping rate ($F_{2,23} = 2.16$; $P = 0.120$) or pinch-grip strength ($F_{2,23} = 0.720$; $P = 0.498$; **Table 1**). We also found no significant effect of genotype on LMT ($F_{2,23} = 0.003$; $P = 0.996$; **Table 1**); similarly, there was no significant effect of genotype ($F_{1,23} = 2.23$; $P = 0.130$) or genotype \times intensity ($F_{6,42} = 0.60$; $P = 0.605$) on baseline MEP amplitudes (**Supplementary Table 1** online). A repeated-measures analysis of variance revealed a significant effect of the genotype \times training interaction on FDI map area ($F_{2,23} = 4.49$; $P = 0.022$). Val/Val subjects showed a significant increase in mean FDI map area after training that was not observed in Val/Met and Met/Met subjects (**Fig. 1a,b**). We found a significant main effect of genotype on percentage change in MEP amplitude at 110% ($F_{2,23} = 13.19$; $P = 0.0002$), 130% ($F_{2,23} = 5.39$; $P = 0.012$) and 150% LMT ($F_{2,23} = 5.50$; $P = 0.011$): Val/Val subjects showed a significantly greater mean percentage increase in post-training MEP amplitude than Val/Met and Met/Met subjects at all three stimulation levels (**Fig. 2a**). Further, we found a significant effect of the genotype \times training interaction on normalized map volume ($F_{2,23} = 6.95$; $P = 0.004$): Val/Val subjects showed a significant post-training increase in mean map volume that was not observed in Val/Met or Met/Met subjects (**Fig. 2b**). Finally, we found a significant effect of genotype ($F_{2,23} = 4.63$; $P = 0.020$) on the net shift in the center of gravity: Val/Val subjects showed a significantly greater mean shift in center of gravity after training than Val/Met and Met/Met subjects (**Fig. 2c**).

Although we observed no baseline differences in corticospinal output or motor map area between Val and Met subjects, a brief period of motor training enhanced corticospinal output and increased motor map area in Val/Val but not Val/Met or Met/Met subjects; the Val/Met and Met/Met subjects actually showed some training effects in the opposite direction. Thus, the physiological consequences of this *BDNF* polymorphism may not manifest in the basal state but only become evident in response to behaviorally driven increases in neural activity. This is consistent with *in vitro* studies showing that transfection of neurons with the *BDNF* met allele does not affect constitutive *BDNF* secretion but does reduce *BDNF* secretion in response to neuronal stimulation⁷. This is also concordant with the observation that in mice lacking the *Bdnf* gene, baseline synaptic physiology is normal but long-term potentiation of synaptic responses after neuronal stimulation is impaired¹². Further, in the current cohort, the presence of even a single

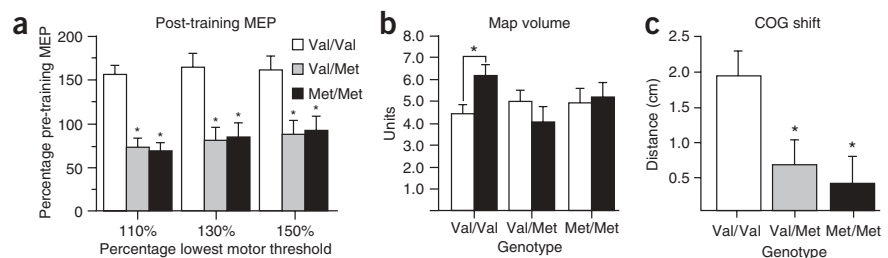


Figure 2 Changes in MEP amplitude, map volume and center of gravity with training. **(a)** Mean (\pm s.e.m.) percentage of pretraining MEP amplitudes observed after training (that is, $(\text{MEP}_{\text{post}}/\text{MEP}_{\text{pre}}) \times 100$) at 110%, 130% and 150% of lowest motor threshold (LMT). Changes in subthreshold MEPs (90% LMT) were not included owing to the inability to reliably evoke measurable MEPs. **(b)** Mean (\pm s.e.m.) normalized map volume. **(c)** Mean (\pm s.e.m.) center of gravity (COG) shift ($*P < 0.05$, Fisher's protected test). There was no significant effect of the sex \times genotype \times intensity interaction on the change in MEP amplitude ($F_{6,36} = 0.74$; $P = 0.45$), on map volume ($F_{2,20} = 0.121$; $P = 0.32$) or on the change in COG ($F_{2,20} = 0.05$; $P = 0.94$).

met allele was sufficient to modify changes in corticospinal output and map organization. This is consistent with the finding that introduction of a single met allele interferes with BDNF secretion *in vitro*⁷.

Notably, there were no differences between the different genotypes on the three fine-motor tasks used in this experiment. Detecting differences in motor performance might require more detailed motor testing to include measures of new, skilled movement. Indeed, cognitive differences observed in subjects with the polymorphism are not generalized, being undetectable on many cognitive tests^{8,13}. The present results do, however, demonstrate that a single-nucleotide missense polymorphism in the *BDNF* gene is associated with modified experience-dependent plasticity in corticospinal output. These findings may have clinical implications, given the central role of BDNF to CNS repair after injury¹⁴.

Note: Supplementary information is available on the Nature Neuroscience website.

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COMPETING INTERESTS STATEMENT

The authors declare that they have no competing financial interests.

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